REMARKS

Claims 173-194, 196-203, 205-211, and 231-232 are currently pending. Claims 173 and 207 have been amended. The amendments to the claims do not constitute new matter.

The Examiner has provisionally rejected claims 173-194, 196-203, 205-211, and 231 under the judicially created doctrine of obviousness-type double patenting over claims 153-173 of copending U.S. Patent Application No. 10/729,056. The Examiner has rejected claims 173-194, 196-203, 205-211, and 231 under the judicially created doctrine of obviousness-type double patenting over claim 8 of U.S. Patent No. 6,410,587. The Examiner has rejected claims 173-181 and 207-211 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner has rejected claims 173-181, 205-211, and 231 under 35 U.S.C. § 103(a) as being obvious over the abstract of Sawada *et al.* (Pharmacometrics, 1992, 44:357-373) ("Sawada"). The Examiner has rejected claims 182-194, 196-203, 205, and 205 over the abstract of Warri (Sarja Ser D Medica Odontologica 133) ("Warri"). For the reasons detailed below, the rejections should be withdrawn and the claims allowed to issue. Entry of the foregoing amendments is respectfully requested.

Double Patenting

The Examiner has provisionally rejected claims 173-194, 196-203, 205-211, and 231 under the judicially created doctrine of obviousness-type double patenting over claims 153-173 of copending U.S. Patent Application No. 10/729,056. The Examiner asserts that the "copending application teaches the mechanisms of action or biological pathways presently claimed by Applicants and renders obvious the diseased [sic] claimed in the instant application." Applicants

will consider the submission of a terminal disclaimer upon notification of allowable subject matter in U.S. Application No. 10/729,056.

The Examiner has rejected claims 173-194, 196-203, 205-211, and 231 under the judicially created doctrine of obviousness-type double patenting over claim 8 of U.S. Patent No. 6,410,587 ("the '587 patent"). Applicants submit that the present invention is not obvious in view of claim 8 of the '587 patent because formula I of the present invention describes a compound that is not encompassed by the formula disclosed in claim 8 of the '587 patent. Applicants would like to draw the Examiner's attention to group R3 of formula I of the present invention, which corresponds to group R9 of the formula of claim 8 of the '587 patent. While R3 is disclosed to be either an ethyl or a chloroethyl, R9 is disclosed to be a cyclic group of various varieties, or a $(C_1\text{-}C_4)$alkoxycarbonyl$(C_1\text{-}C_6)$alkyl group. Therefore, the claims of the present invention are patentably distinct from claim 8 of the '587 patent, because the compounds encompassed by formula I of the present invention are not the same as the compounds encompassed by the formula of claim 8 of the '587 patent. Furthermore, the '587 does not provide any suggestion or motivation to modify R9 to match R3 of formula I of the present invention. Even if one assumes that R9 and R3 were the same, the '587 patent does not provide any suggestion or motivation to specifically select the substituents utilized in formula I of the present invention; without a specific suggestion or motivation, the present application cannot be obvious in view of the '587 patent. See MPEP § 2144.08 ("The fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie*

case of obviousness.").[1] Accordingly, Applicants submit that the presently claimed invention is patentably distinct from claim 8 of the '587 patent.

In view of the foregoing, reconsideration and withdrawal of the double patenting rejections are respectfully requested.

The Claims Are Enabled

The Examiner has rejected claims 173-181 and 207-211 under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner asserts that the specification "does not reasonably provide enablement for '**preventing** a cardiovascular or vascular indication.'" (Emphasis in original).

Applicants note that claims 173 and 207 have been amended to delete reference to "preventing" a cardiovascular or vascular indication. Accordingly, Applicants submit that the Examiner's rejection has been obviated, and that the claims, as amended, are enabled by the specification. Applicants respectfully request that the rejections be withdrawn.

The Claims Are Not Obvious In View Of Sawada

The Examiner has rejected claims 173-181, 205-211, and 231 under 35 U.S.C. § 103(a) as being obvious over the abstract of Sawada *et al.* (Pharmacometrics, 1992, 44:357-373) ("Sawada"). The Examiner states that it "would have been obvious to one of ordinary skill in the art to employ toremifene citrate (NK622) in 0.1 mg/kg or more including 10 mg/kg (cytostatic dose) to a mammal at risk or afflicted with cardiovascular or vascular indication."

[1] Applicants note that obviousness-type double patenting rejections are analogous to rejections under 35 U.S.C. § 103, except that the patent in question (*i.e.*, the '587 patent) is not considered prior art. Thus, arguments directed to *prima facie* obviousness may be employed to address the double patenting rejection, and do not constitute an admission or acknowledgement that the cited reference is prior art. See MPEP § 804.

Applicants submit that the Examiner has not established a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, the Examiner must meet three criteria. The Examiner must establish that (1) there is some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there is a reasonable expectation of success; and (3) the prior art reference (or references when combined) teach or suggest all the claim limitations. See MPEP §§ 706.02(j) and 2143. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q2d 1438 (Fed. Cir. 1991).

Applicants enclose herewith a translated copy of Sawada as Exhibit A. Applicants respectfully disagree with the Examiner, and note that Sawada primarily investigates toxicity of toremifene. Sawada provides no information regarding recommended dosages, but merely tests a broad range of dosages to determine toxicity. See Sawada at page 2 of translation. At best, Sawada states that "the 0.01 mg/kg dose can be considered close to the non-effective dose level." See Sawada at page 16 of translation. Furthermore, Sawada shows that toremifene demonstrated various toxic effects at the different doses, and caused an abnormal estrous cycle even at very low doses (0.1 mg/kg). See Sawada at pages 8-12 of translation. While Sawada does disclose the lowering of total serum cholesterol by toremifene, Sawada does not provide any data linking this cholesterol-lowering effect to any cardiovascular or vascular indication, nor to decreased lumen diameter.

With this in mind, Applicants submit that the Examiner has not shown a sufficient suggestion or motivation to utilize toremifene to treat cardiovascular or vascular indications.

Applicants note that the specification defines cardiovascular and vascular indications to those that are associated with decreased lumen diameter. See page 3, lines 5-7. As noted in the specification, the mechanisms behind decreases in lumen diameter, as exemplified by an atherosclerotic lesion, are varied and complex; they are not narrowed down to a single cause. See page 41, line 14 to page 43, line 9. While Sawada may show that toremifene decreases total serum cholesterol, it provides no evidence that Sawada would have any effect on lumen diameter. Accordingly, a person of ordinary skill in the art would not be motivated to utilize toremifene to treat a cardiovascular or vascular indication characterized by decreases in lumen diameter, based upon the teachings of Sawada. Furthermore, Sawada tests a broad range of doses for toxicity, and does not provide any teaching or motivation to how much toremifene to use to treat a cardiovascular or vascular indication characterized by a decreased lumen diameter. Absent such a specific teaching in Sawada, there is insufficient suggestion or motivation; the "fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness." MPEP § 2143.01.

Sawada does not teach all of the limitations of the present claims. Sawada does not teach, nor even refers to, the utility of toremifene for the treatment of any cardiovascular or vascular indications characterized by decreased lumen diameter. As noted above, Sawada also does not teach the administration of an effective amount, but merely discloses a broad range of doses for a toxicity study. Accordingly, the Examiner has not established a *prima facie* case of obviousness. See MPEP § 2143.03.

Based upon the foregoing, Applicants submit that the present invention is non-obvious in view of Sawada, and respectfully request that the rejection be withdrawn.

The Claims Are Not Obvious In View Of Warri

The Examiner has rejected claims 182-194, 196-203, 205, and 206 over the abstract of Warri (cite) ("Warri"). The Examiner asserts that in light of Warri, it would have been obvious "to employ toremifene in a mammal to increase the level of TGF-beta.... in order to achieve the expected benefit of treating breast cancer in mammal [sic] in any population." Applicants enclose herewith a complete copy of Warri as Exhibit B.

Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness, because there is insufficient suggestion or motivation to modify Warri to reach the present invention. The Examiner asserts that it would have been obvious to utilize toremifene to treat cardiovascular or vascular indications characterized by decreased lumen diameter because Warri teaches the beneficial effects of toremifene on breast cancer cells. However, Warri does not provide any link between breast cancer and cardiovascular or vascular indications characterized by decreased lumen diameter. In fact, Warri does not disclose any effects of toremifene on cardiovascular or vascular indications characterized by decreased lumen diameter, nor the effect of increased TGF-beta on such an indication. Based upon Warri, a person of ordinary skill in the art would not have a suggestion or motivation to utilize toremifene to treat cardiovascular or vascular indications characterized by decreased lumen diameter, because Warri provides no link between toremifene and cardiovascular or vascular indications characterized by decreased lumen diameter.

A person of ordinary skill in the art would not have a reasonable expectation of success based upon the teachings of Warri. Warri does not teach administration of toremifene to treat cardiovascular or vascular indications characterized by decreased lumen diameter. Warri discloses only dosages for the potential treatment of breast cancer. A person of ordinary skill in

the art would not be able to assume that doses effective to treat breast cancer would also be effective to treat cardiovascular or vascular indications characterized by decreased lumen diameter. Absent a specific teaching of how much toremifene to use, a person of ordinary skill in the art would not have a reasonable expectation of success in using toremifene to treat cardiovascular or vascular indications characterized by decreased lumen diameter. MPEP § 2143.02.

Applicants note that Warri does not teach administration of toremifene to "a mammal in need thereof," because Warri utilizes breast cancer cells excised from mice. See Warri at page 35. Accordingly, Warri does not teach all of the limitations of the present invention.

Based upon the foregoing, Applicants submit that the present invention is non-obvious in view of Warri, and respectfully request that the rejection be withdrawn.

CONCLUSION

Entry of the foregoing amendments and remarks into the file of the above-identified application is respectfully requested. The Applicant believes that the inventions described and defined by claims 173-194, 196-203, 205-211, and 231 are patentable over the rejections of the Examiner. Withdrawal of all rejections and reconsideration of the amended claims is requested. An early allowance is earnestly sought.

Respectfully submitted,

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